

Hypoallergenic Foods in Pediatric Nutrition: A Comprehensive Review

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ABSTRACT

Background: Food allergies are a growing concern in pediatric populations, with cow's milk protein allergy (CMPA) being the most prevalent. CMPA affects 2–3% of children globally and can lead to poor nutritional status, impaired growth, and reduced quality of life. Hypoallergenic foods, particularly extensively hydrolyzed formulas (EHFs) and amino acid-based formulas (AAFs), are essential dietary interventions for managing CMPA and preventing allergy development. **Objective:** This review evaluates hypoallergenic foods' efficacy, safety, and clinical applications in pediatric allergy prevention and management. **Methods:** A systematic literature review was conducted using peer-reviewed articles, clinical studies, and guidelines related to hypoallergenic formulas, their clinical outcomes, and allergy prevention strategies in children. **Results:** EHFs and AAFs are proven effective in managing cow's milk protein allergy (CMPA) and improving growth outcomes. EHFs are recommended for mild-to-moderate cases, while AAFs are the standard for severe allergies. Emerging evidence suggests that probiotic-supplemented formulas may enhance tolerance. Clinical guidelines emphasize early intervention in high-risk infants to reduce allergy development. **Conclusion:** Hypoallergenic foods play a critical role in pediatric allergy management, with EHFs and AAFs as key dietary interventions. Continued research is needed to improve formula composition and long-term outcomes.

Keywords: hypoallergenic foods; pediatric nutrition; extensively hydrolyzed formulas; amino acid-based formulas; food allergies.

INTRODUCTION

Food allergies are a growing public health concern, especially among pediatric populations, where they impose significant burdens on healthcare systems and families. Cow's milk protein allergy (CMPA) remains the most common food allergy in infants and young children, affecting approximately 2–3% globally [1,2]. CMPA results from an immune-mediated response to cow's milk proteins, including casein and whey, and can manifest through gastrointestinal, dermatological, and respiratory symptoms, leading to impaired growth, nutritional deficiencies, and reduced quality of life [3,4].

The cornerstone of CMPA management is strict avoidance of cow's milk proteins while ensuring adequate nutrition. Hypoallergenic formulas play a pivotal role in this management, particularly in formula-fed infants. There are two primary types of hypoallergenic formulas, Extensively Hydrolyzed Formulas (EHFs) and Amino Acid-Based Formulas (AAFs). Extensively Hydrolyzed Formulas (EHFs) contain proteins enzymatically broken down into smaller peptides that reduce allergenicity, making

them suitable for mild-to-moderate CMPA cases [2,5]. By contrast, Amino Acid-Based Formulas (AAFs) consist of free amino acids and are entirely non-allergenic, making them the gold standard for managing severe, refractory CMPA or multiple food allergies [5,6].

In recent years, probiotic-supplemented EHFs have emerged as an innovative approach to CMPA management. Probiotics, such as *Lactobacillus rhamnosus* GG, enhance gastrointestinal tolerance, support gut microbiota balance, and promote immune modulation, which may accelerate the acquisition of tolerance to cow's milk proteins [7,8]. Clinical studies have shown that probiotic-supplemented EHFs not only improve symptoms but also contribute to improved gut health outcomes compared to standard EHFs [8,9].

Beyond management, hypoallergenic formulas play a role in allergy prevention, particularly in high-risk infants. Research indicates that introducing EHFs during the first 4–6 months of life may reduce the risk of developing CMPA and atopic dermatitis,

particularly in children with a family history of allergies [4,10].

Despite their efficacy, challenges remain regarding the widespread use of hypoallergenic foods. These include the high costs of AAFs, limited availability in low-resource settings, and inconsistent guidelines regarding formula selection and testing standards [5,6,10]. Additionally, long-term effects on growth, immune tolerance, and allergy prevention require further investigation through longitudinal studies [6,9].

This review evaluates the latest evidence on the clinical efficacy, safety, and role of hypoallergenic formulas—specifically EHF and AAF—in managing and preventing CMPA. Emerging trends, such as probiotic-supplemented formulas and novel dietary compositions, are also discussed to highlight advancements in pediatric allergy management.

METHODS

This literature review was conducted to evaluate the efficacy, safety, and clinical applications of hypoallergenic foods, specifically extensively hydrolyzed formulas (EHF) and amino acid-based formulas (AAF), in the management and prevention of cow's milk protein allergy (CMPA) in pediatric populations.

Search Strategy

A comprehensive search of peer-reviewed scientific literature was conducted to identify studies relevant to hypoallergenic formulas and their role in managing and preventing cow's milk protein allergy (CMPA) in pediatric populations. The search utilized three major databases: PubMed, Scopus, and Web of Science, and was limited to articles published between 2014 and 2024 to ensure the inclusion of up-to-date evidence.

To identify relevant studies, a combination of keywords and Medical Subject Headings (MeSH) terms was employed.

The search terms included: "Hypoallergenic formulas," "Extensively hydrolyzed formulas (EHFs)," "Amino acid-based formulas (AAFs)," "Cow's milk protein allergy (CMPA)," "Pediatric food allergies," "Allergy prevention," and "Probiotic-supplemented formulas."

The selection process focused on identifying studies that evaluated the clinical efficacy, safety, and preventive role of hypoallergenic formulas, particularly EHF and AAF, in CMPA management. Studies on emerging innovations, such as probiotic-supplemented formulas, were also included to capture advancements in this area of pediatric allergy care.

Study Selection

Titles and abstracts of all identified articles were screened for relevance. Full-text reviews of selected articles were conducted to ensure alignment with the inclusion criteria. The search process was conducted independently by two reviewers to minimize bias. Any discrepancies in study selection were resolved through discussion and consensus.

Quality Assessment

The quality of the included studies was assessed using standard tools such as the Cochrane Risk of Bias Tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for observational studies. Only studies with low or moderate risk of bias were included in the final analysis.

RESULTS

Types of Hypoallergenic Foods

The two primary types of hypoallergenic formulas used in pediatric nutrition for managing cow's milk protein allergy (CMPA) are extensively hydrolyzed formulas (EHF) and amino acid-based formulas (AAF). Recent advancements have also led to the inclusion of probiotic-supplemented EHF to improve gastrointestinal tolerance and immune function.

TABLE 1: Types of Hypoallergenic Foods.

Formula Type	Composition	Indications	Clinical Evidence
Extensively Hydrolyzed Formula (EHF)	Partially broken-down peptides	Mild-to-moderate CMPA	Proven $\geq 90\%$ tolerance; supports normal growth
Amino Acid-Based Formula (AAF)	Free amino acids (completely non-allergenic)	Severe CMPA or failure of EHF	100% tolerance; resolves symptoms cases
Probiotic-Supplemented EHF	EHF + <i>Lactobacillus rhamnosus GG</i>	CMPA management + improved gut health	Reduces allergic symptoms; improves gut microbiota

Clinical Efficacy and Safety

Both extensively hydrolyzed formulas (EHFs) and amino acid-based formulas (AAFs) demonstrate high efficacy and safety profiles in managing cow's milk protein allergy (CMPA). Clinical studies have shown that EHFs achieve $\geq 90\%$ tolerance in infants with mild-to-moderate CMPA, making them a suitable first-line intervention for these cases [1,3]. In contrast, AAFs, which are completely non-allergenic, are highly effective in achieving 100% tolerance for severe or refractory CMPA, particularly in infants who do not respond to EHFs or have multiple food allergies [4,5].

These findings highlight the importance of selecting the appropriate formula based on the severity of the allergy and the individual needs of the child. Both formulas contribute to significant symptom resolution. EHFs have been shown to alleviate gastrointestinal symptoms, skin reactions such as eczema, and respiratory distress within 2–4 weeks of use [2]. In cases where EHFs fail, AAFs provide rapid and complete symptom relief, ensuring effective management of severe allergic manifestations [4]. In addition to their efficacy in symptom management, both EHFs and AAFs support normal growth and development.

Studies demonstrate that children receiving these formulas achieve growth parameters, including weight and height, that are comparable to those of healthy, non-allergic peers. This underscores the nutritional adequacy of hypoallergenic formulas in maintaining appropriate growth trajectories in infants and young children with CMPA [3,6].

Allergy Prevention

Hypoallergenic formulas, particularly extensively hydrolyzed formulas (EHFs), play a significant role in the primary prevention of cow's milk protein allergy (CMPA) and other allergic conditions in high-risk infants, such as those with a family history of allergies. Clinical studies have demonstrated that introducing EHFs during the first 4–6 months of life can reduce the incidence of atopic dermatitis by up to 50% when compared to infants fed standard cow's milk formulas. This highlights the potential of EHFs as an early dietary intervention for preventing the development of allergic diseases in susceptible populations [6,7]. In addition to their preventive effects, probiotic-supplemented EHFs, particularly those containing *Lactobacillus rhamnosus* GG, offer added benefits through their ability to modulate gut microbiota. Probiotics improve the balance of gut microorganisms, which is crucial for enhancing immune function and promoting oral tolerance to cow's milk proteins. This combination not only reduces allergic inflammation but also accelerates the acquisition of tolerance, offering a promising strategy for CMPA prevention and long-term immune health [5,8]. Those containing *Lactobacillus rhamnosus* GG, offer added benefits through their ability to modulate gut microbiota. Probiotics improve the balance of gut microorganisms, which is crucial for enhancing immune function and promoting oral tolerance to cow's milk proteins. This combination not only reduces allergic inflammation but also accelerates the acquisition of tolerance, offering a promising strategy for CMPA prevention and long-term immune health [5,8].

TABLE 2: Allergy Prevention.

Study Focus	Formula Type	Findings
CMPA prevention in high-risk infants	Extensively Hydrolyzed Formula (EHF)	Reduced atopic dermatitis incidence by ~50%
Gut health improvement	Probiotic-Supplemented EHF	Enhanced gut microbiota; reduced symptoms
Allergy resolution in severe cases	Amino Acid-Based Formula (AAF)	Complete resolution of allergic reactions

Challenges in Clinical Use

Despite their proven efficacy, the clinical application of hypoallergenic formulas faces several challenges that can limit their widespread use. One of the most significant barriers is the high cost of amino acid-based formulas (AAFs), which are substantially more expensive than extensively hydrolyzed formulas (EHFs). This creates economic challenges, particularly in low-resource settings where affordability is a major concern and access to specialized formulas is limited [4,9].

In addition to cost, limited accessibility remains a critical issue in certain regions. Regulatory inconsistencies, distribution challenges, and healthcare

disparities further restrict the availability of hypoallergenic formulas, preventing many families from accessing the appropriate dietary interventions for managing cow's milk protein allergy (CMPA) [10]. Another factor impacting the effectiveness of these formulas is adherence. Limited parental awareness of CMPA management, combined with concerns about the palatability of certain hypoallergenic formulas, can hinder long-term compliance with dietary recommendations. Poor adherence can compromise the clinical outcomes and nutritional status of affected infants, highlighting the need for parental education and support programs to ensure the successful implementation of dietary interventions [8].

Emerging Trends

Recent advancements in hypoallergenic formulas offer promising strategies for enhancing the management of cow's milk protein allergy (CMPA). One such innovation involves the use of probiotic-supplemented formulas, particularly those containing strains like *Lactobacillus rhamnosus* GG. Combining probiotics or prebiotics with extensively hydrolyzed formulas (EHFs) has demonstrated significant potential in enhancing immune tolerance, modulating gut health, and reducing allergic inflammation. These formulas help balance gut microbiota, a critical factor in immune development and oral tolerance acquisition, ultimately improving clinical outcomes in infants with CMPA [5,8]. In addition to probiotics, research into alternative protein sources has expanded options for CMPA management. Hydrolyzed rice-based formulas and other plant-derived protein formulas are emerging as effective substitutes for traditional cow's milk-derived formulas. These alternatives are particularly beneficial for infants with multiple food allergies or for families adhering to cultural, dietary, or ethical preferences [9,10]. Furthermore, advancements in personalized nutrition hold significant potential for optimizing CMPA management. By identifying genetic and immunological biomarkers, clinicians may soon be able to tailor hypoallergenic formula selection to the individual needs of each patient. This precision approach can improve treatment outcomes, enhance tolerance development, and reduce the trial-and-error process often associated with formula selection [6,10].

DISCUSSION

This review highlights the critical role of hypoallergenic formulas, particularly extensively hydrolyzed formulas (EHFs) and amino acid-based formulas (AAFs), in managing and preventing cow's milk protein allergy (CMPA) in pediatric populations. The discussion examines the efficacy, safety, emerging trends, and challenges associated with hypoallergenic foods.

Clinical Efficacy and Safety

The findings confirm that extensively hydrolyzed formulas (EHFs) and amino acid-based formulas (AAFs) are highly effective in managing cow's milk protein allergy (CMPA) while ensuring optimal growth outcomes in affected infants.

EHF are considered the first-line intervention for mild-to-moderate CMPA. By minimizing allergenicity through the enzymatic breakdown of proteins into smaller peptides, EHFs achieve $\geq 90\%$ tolerance rates in affected infants [1,2]. Clinical trials have demonstrated that EHFs significantly resolve symptoms, including gastrointestinal issues, skin reactions (such as eczema), and respiratory distress, typically within 2–4 weeks of formula introduction. Importantly, EHFs maintain nutritional adequacy, making them a suitable and effective choice for most infants with CMPA [3,4].

For severe or refractory cases of CMPA, AAFs serve as the gold standard. These formulas consist entirely of free amino acids, making them completely non-

allergenic and ideal for infants who do not respond to EHFs or those with multiple food allergies or eosinophilic gastrointestinal disorders. AAFs provide rapid and complete symptom relief, ensuring effective management of even the most complex allergic presentations [5,6].

Both EHFs and AAFs play a crucial role in supporting normal growth and development in infants with CMPA. Studies have consistently shown that children fed these formulas achieve weight and height parameters comparable to their non-allergic peers, underscoring their nutritional adequacy. However, despite their proven efficacy, the high cost of AAFs remains a significant barrier to widespread adoption, particularly in low-resource settings where access to specialized formulas is limited [4,7].

Role of Hypoallergenic Formulas in Allergy Prevention

An important clinical application of extensively hydrolyzed formulas (EHFs) lies in the primary prevention of allergies for high-risk infants, particularly those with a family history of atopy. Studies have demonstrated that introducing EHFs during the first 4–6 months of life can reduce the risk of atopic dermatitis and cow's milk protein allergy (CMPA) by up to 50% when compared to infants fed standard cow's milk formulas. This highlights the potential of EHFs as an early dietary intervention to mitigate the development of allergic conditions in susceptible infants [6,8]. Further advancements in this area include the use of probiotic-supplemented EHFs, particularly those containing *Lactobacillus rhamnosus* GG. These formulas offer additional benefits by improving gut microbiota diversity and enhancing immune modulation. The combination of probiotics and EHFs helps to reduce inflammation and accelerate oral tolerance acquisition to cow's milk proteins, contributing to improved allergy prevention outcomes [8,9].

However, while early interventions with hypoallergenic formulas show considerable promise, further research is needed to confirm their long-term efficacy. Evidence suggests that the preventive effects observed during formula use may diminish once the hypoallergenic formulas are discontinued. Long-term follow-up studies are essential to determine whether the early introduction of EHFs provides sustained protection against allergic diseases throughout childhood and beyond [6,10].

Challenges in Clinical Implementation

Despite their proven efficacy and safety, several challenges limit the clinical use of hypoallergenic formulas, particularly extensively hydrolyzed formulas (EHFs) and amino acid-based formulas (AAFs). One major barrier is the high cost of AAFs, which makes them prohibitively expensive for many families, creating significant economic disparities in access. Although EHFs are comparatively more affordable, they remain out of reach for families in low-resource settings, where economic and healthcare constraints further exacerbate the issue [5,7].

Another critical challenge is the limited availability of hypoallergenic formulas. Regulatory barriers, coupled with inconsistent distribution systems, restrict access to these specialized formulas in certain regions, particularly in underserved and rural areas. This lack of availability makes it difficult for families to obtain the appropriate dietary interventions for managing cow's milk protein allergy (CMPA) [9].

Additionally, parental awareness and adherence pose significant obstacles. Poor understanding of CMPA management and limited awareness of the role and benefits of hypoallergenic formulas can undermine their use. Concerns about the palatability of certain formulas further reduce adherence to prescribed dietary interventions, compromising their clinical effectiveness [6,10]. These barriers emphasize the need for healthcare systems to implement subsidized programs that make hypoallergenic formulas more accessible to families, especially in low-resource settings. Furthermore, educational initiatives aimed at raising parental awareness about CMPA management and the importance of hypoallergenic formulas are essential to ensure consistent adherence and improve clinical outcomes for affected infants.

Emerging Trends and Future Directions

Recent advancements in the development of hypoallergenic formulas aim to address their current limitations while improving clinical efficacy and accessibility. One promising innovation is the introduction of probiotic-supplemented formulas, particularly those enriched with strains such as *Lactobacillus rhamnosus* GG and *Bifidobacterium breve*. The addition of probiotics to extensively hydrolyzed formulas (EHFs) has demonstrated significant benefits, including the modulation of gut microbiota, reduction of inflammatory responses, and improvement in gastrointestinal outcomes. This approach supports immune system maturation and accelerates oral tolerance acquisition, positioning probiotic-enriched formulas as an important advancement in the management of cow's milk protein allergy (CMPA) [8,10].

In addition to probiotics, the use of alternative protein sources is gaining attention. Hydrolyzed rice-based formulas and other plant-derived protein alternatives are emerging as effective substitutes for cow's milk-derived formulas. These options provide critical nutritional support for infants with multiple food allergies and are particularly valuable for families with cultural, dietary, or ethical preferences [9,11].

Another significant advancement is the potential for personalized nutrition in CMPA management. Advances in the identification of genetic and immunological biomarkers may soon allow for the tailoring of hypoallergenic formula selection to individual patient profiles. This precision-based approach has the potential to optimize clinical outcomes, reduce the need for trial-and-error formula selection, and improve the overall

effectiveness of CMPA management [7,12]. Efforts are also underway to develop cost-effective solutions that enhance the accessibility of hypoallergenic formulas, particularly amino acid-based formulas (AAFs) and EHF. Research focused on reducing production costs aims to make these specialized formulas more affordable, especially in resource-limited settings where economic constraints often limit their use [5,9].

Clinical Implications

The evidence presented in this review highlights several important implications for clinical practice in managing cow's milk protein allergy (CMPA). Clinicians should prioritize the use of extensively hydrolyzed formulas (EHFs) as the first-line intervention for infants with mild-to-moderate CMPA due to their proven efficacy and nutritional adequacy. In contrast, amino acid-based formulas (AAFs) should be reserved for severe or refractory cases where EHF fail to provide symptom relief, particularly in infants with multiple food allergies or eosinophilic gastrointestinal disorders.

For infants presenting with gastrointestinal symptoms or those at high risk of developing allergies, probiotic-supplemented formulas should be considered. These formulas, which incorporate strains such as *Lactobacillus rhamnosus* GG, not only alleviate gastrointestinal discomfort but also play a role in allergy prevention by enhancing gut microbiota balance and supporting immune tolerance acquisition.

The early identification of high-risk infants—such as those with a family history of atopy—and the timely initiation of hypoallergenic formulas are critical steps in reducing the incidence of allergic diseases, including CMPA and atopic dermatitis. Early intervention can significantly improve long-term health outcomes and reduce the burden of allergic conditions in pediatric populations.

Furthermore, to address disparities in access to these specialized formulas, policymakers must take action to overcome economic barriers. Efforts should focus on developing strategies to ensure the equitable availability of hypoallergenic formulas, particularly in underserved regions where cost and accessibility remain significant challenges.

CONCLUSIONS

Hypoallergenic formulas, particularly EHF and AAF, are critical for managing and preventing CMPA in pediatric populations. EHF provide effective, first-line management for mild-to-moderate cases, while AAF remain the gold standard for severe allergies. The addition of probiotics and emerging trends in formula composition offer promising advances to enhance clinical outcomes. Addressing challenges such as cost and access will be essential for optimizing the widespread implementation of these formulas. Further research is needed to explore long-term outcomes, personalized approaches, and cost-effective solutions to improve pediatric allergy management globally.

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REFERENCES

- [1] Meyer R, Carey M, Turner P, Meharg A. Low inorganic arsenic in hydrolysed rice formula used for cow's milk protein allergy. *Pediatr Allergy Immunol.* 2018;29(6):1-7. DOI: 10.1111/pai.12913.
- [2] D'Auria E, Salvatore S, Acunzo M, et al. Hydrolysed formulas in the management of cow's milk allergy: New insights, pitfalls and tips. *Nutrients.* 2021;13(8):2762. DOI: 10.3390/nu13082762.
- [3] Anania C, Martinelli I, Brindisi G, et al. Hydrolyzed rice formula: An appropriate choice for the treatment of cow's milk allergy. *J Clin Med.* 2022;11(16):4823. DOI: 10.3390/jcm11164823
- [4] Ribes-Koninckx C, Amil-Dias J, Espín B, et al. The use of amino acid formulas in pediatric patients with allergy to cow's milk proteins: Recommendations. *Front Pediatr.* 2023;11:1110380. DOI: 10.3389/fped.2023.1110380
- [5] Levin M, Blackhurst D, Kirstein F, et al. Residual allergenicity of amino acid-based and extensively hydrolysed cow's milk formulas. *S Afr Med J.* 2017;107(9):763-767. DOI: 10.7196/SAMJ.2017.v107i9.12137
- [6] Dupont C, Bocquet A, Tomé D, et al. Hydrolyzed rice protein-based formulas, a vegetal alternative in cow's milk allergy. *Nutrients.* 2020;12(9):2654. DOI: 10.3390/nu12092654
- [7] Rossetti D, Cucchiara S, Morace A, Leter B, Oliva S. Hypoallergenicity of a thickened hydrolyzed formula in children with cow's milk allergy. *World J Clin Cases.* 2019;7(16):2256-2268. DOI: 10.12998/wjcc.v7.i16.2256
- [8] Meyer R, Smith C, Sealy L, Mancell S, Marino L. The use of extensively hydrolysed and amino acid feeds beyond cow's milk allergy: A national survey. *J Hum Nutr Diet.* 2020;1-10. DOI: 10.1111/jhn.12794
- [9] Dupont C, Kalach N, Soulaïnes P, et al. A thickened amino-acid formula in infants with cow's milk allergy failing to respond to protein hydrolysate formulas. *Pediatr Drugs.* 2014;16(6):513-522. DOI: 10.1007/s40272-014-0097-x
- [10] Paquete A, Martins R, Connolly M, et al. Managing cow's milk protein allergy in Indonesia: A cost-effectiveness analysis of hypoallergenic milk formulas. *J Health Econ Outcomes Res.* 2022;9:77-85. DOI: 10.36469/001c.36407